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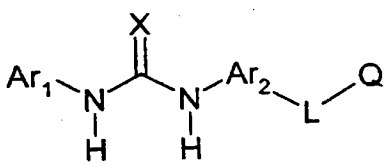
(54) Title: NOVEL PROCESS FOR SYNTHESIS OF HETEROARYL-SUBSTITUTED UREA COMPOUNDS



(I)

(57) Abstract: Disclosed are novel processes and novel intermediate compounds for preparing aryl- and heteroaryl-substituted urea compounds of formula (I) wherein Ar_1, Ar_2, L, Q and X are described herein. The product compounds are useful in pharmaceutic compositions for treating diseases or pathological conditions involving inflammation such as chronic inflammatory diseases.

WO 01/04115 A2

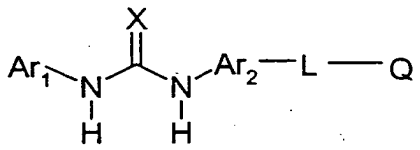
Novel Process for Synthesis of Heteroaryl-substituted Urea Compounds

RELATED APPLICATION DATA

This application claims benefit to US Provisional Application Serial No. 60/143,094, filed July 9, 1999.

TECHNICAL FIELD OF THE INVENTION

This invention relates to novel processes for preparing new aryl-and heteroaryl-substituted urea compounds of formula (I):



(I)

wherein Ar_1, Ar_2, X, L and Q are defined below, which are useful for treating diseases and pathological conditions involving inflammation such as chronic inflammatory disease.

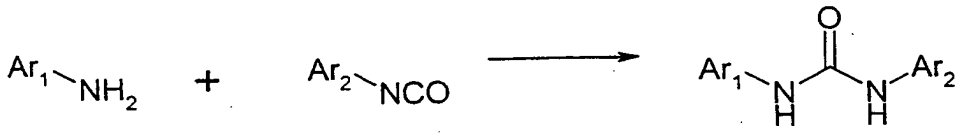
BACKGROUND OF THE INVENTION

Aryl- and heteroaryl-substituted ureas have been described as inhibitors of cytokine production. Examples of such compounds are reported in WO 99/23091 and in WO 98/52558. These inhibitors are described as effective therapeutics in cytokine-mediated diseases, including inflammatory and autoimmune diseases.

A key step in the synthesis of these compounds is the formation of the urea bond. Various methods have been reported to accomplish this. For example, as reported in the

above references, an aromatic or heteroaromatic amine, II, may be reacted with an aromatic or heteroaromatic isocyanate III to generate the urea IV (Scheme I)

Scheme I

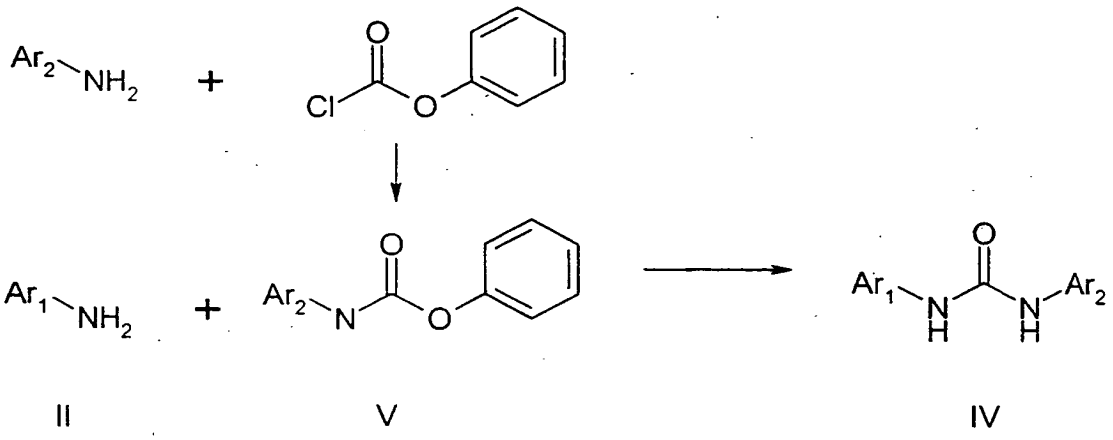


II III IV

If not commercially available, one may prepare the isocyanate III by reaction of an aryl or heteroaryl amine Ar_2NH_2 with phosgene or a phosgene equivalent, such as bis(trichloromethyl) carbonate (triphosgene) (P. Majer and R. S. Randad, J. Org. Chem. 1994, 59, 1937) or trichloromethyl chloroformate (diphosgene). K. Kurita, T. Matsumura and Y. Iwakura, J. Org. Chem. 1976, 41, 2070) to form the isocyanate III, followed by reaction with Ar_1NH_2 to provide the urea. Other approaches to forming the urea known in the chemical literature are to form a carbamate, as shown in Scheme II below, by reaction of an amine with a chloroformate derivative, such as phenyl chloroformate (B. Thavonekham, Synthesis, 1997, 1189), chloromethyl chloroformate (T. Patonay, E. Patonay-Peli, L Zolnai and F. Mogyorodi, Synthetic Communications, 1996, 26, 4253), p-nitrophenyl chloroformate (J. Gante, Chem. Ber. 1965, 98, 3334), or 2,4,5-trichlorophenyl chloroformate (A. W. Lipkowski, S. W. Tam and P. S. Portoghese, J. Med. Chem. 1986, 29, 1222) to form a carbamate V. This may then be reacted with an aryl or heteroaryl amine (II) to provide urea IV (Scheme II- reaction with phenyl chloroformate shown). The synthesis of ureas through (phenoxycarbonyl)tetrazole (R. W. Adamiak, J. Stawinski, Tetrahedron Lett. 1977, 1935) or 1,1'-carbonylbisbenzotriazole (A. R. Katritzky, D. P. M. Pleynet and B. Yang, J. Org. Chem. 1997, 62, 4155) has been reported. In addition, preparation of ureas by catalytic carbonation of amines with carbon monoxide or carbon dioxide has been documented in the literature (N. Sonoda, T. Yasuhara, K. Kondo, T. Ikeda and S. Tsutsumi, J. Am. Chem. Soc. 1971, 93, 691; Y. Morimoto, Y. Fujiwara, H. Taniguchi, Y. Hori and Y.

Nagano, Tetrahedron Lett. 1986, 27, 1809). In each of these cases, Ar_1 and Ar_2 may be modified before and/or after the urea formation to produce desired compounds.

Scheme II



Each of the methods described above suffer from one or more disadvantages. For example, phosgene and phosgene equivalents are hazardous and dangerous to use, particularly in large-scale applications. In addition the isocyanate intermediate III is not stable and may undergo decomposition during preparation and storage. The urea formation may be done using a phenyl carbamate, as illustrated in Scheme II and U.S. Application Serial No. 09/484,638. However, the by-product phenol formed in the urea synthesis does not have sufficient water solubility to be easily removed by water washing especially at large scale. Thus it may require multiple washing and several crystallizations to obtain highly pure product. For these reasons these methods are not well-suited for industrial-scale production.

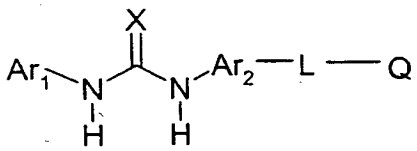
U.S. Application Serial No. 09/484,638 also discloses the synthesis of substituted naphthyl amino intermediates for use in making aryl-and heteroaryl-substituted urea compounds of the formula(I) as described therein. This synthesis begins with 4-aminonapthol which is protected with a Boc (*tert*-butoxycarbonyl) group on the amine

prior to alkylation and deprotection. This procedure is also not amenable to industrial-scale production. The starting 4-aminonaphthol is very expensive and not available in large quantity. In addition the protection and deprotection steps are tedious and add to the expense.

Disclosed herein are novel processes for making the aryl-and heteroaryl-substituted urea compounds of the formula(I) including those disclosed in U.S. Application Serial No. 09/484,638 and novel intermediates useful in such processes.

BRIEF SUMMARY OF THE INVENTION

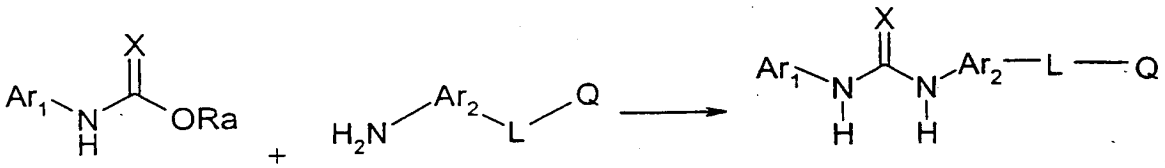
It is therefore an object of this invention to provide a general and cost-effective process for the preparation of the aryl- and heteroaryl-substituted urea compounds of the formula(I) shown below:



(I)

comprising the steps of:

reacting of intermediate of formula (II) with intermediate of formula (IV) to produce the product compound of formula (I):



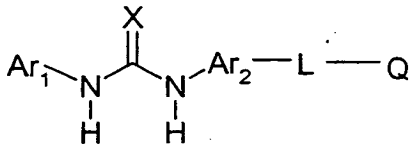
(II) (IV) (I)

wherein Ar_1, Ar_2, L, Q, X and Ra are as described below.

In addition, this invention provides efficient methods for preparing intermediates used in the preparation of preferred cytokine-inhibiting aryl-and heteroaryl-substituted ureas. These processes are especially well-suited for preparation of these compounds on an industrial scale.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to the synthesis of compounds having formula (I):



(I)

wherein:

Ar_1 is a heterocyclic group selected from the group consisting of phenyl, pyridine, pyridone, pyrrole, pyrrolidine, pyrazole, imidazole, oxazole, thiazole, furan and thiophene; wherein Ar_1 is optionally substituted by one or more R_1, R_2 or R_3;

Ar_2 is:

phenyl, naphthyl, quinoline, isoquinoline, tetrahydronaphthyl, tetrahydroquinoline, tetrahydroisoquinoline, benzimidazole, benzofuran, indanyl, indenyl or indole each being optionally substituted with one to three R_2 groups;

L, a linking group, is:

$C_{1\text{-}10}$ saturated or unsaturated branched or unbranched carbon chain;

wherein one or more methylene groups are optionally independently replaced by O,N or S; and

wherein said linking group is optionally substituted with 0-2 oxo groups and one or more C_{1-4} branched or unbranched alkyl optionally substituted by one or more halogen atoms;

or L is a cyclic group which is:

a) a C_{5-8} cycloalkyl or cycloalkenyl optionally substituted with 1-2 oxo groups, 1-3 C_{1-4} branched or unbranched alkyl, C_{1-4} alkoxy or C_{1-4} alkylamino chains;

b) phenyl, furan, thiophene, pyrrole, imidazolyl, pyridine, pyrimidine, pyridinone, dihydropyridinone, maleimide, dihydromaleimide, piperdine, piperazine or pyrazine each being optionally independently substituted with 1-3 C_{1-4} branched or unbranched alkyl, C_{1-4}alkoxy, hydroxy, cyano, mono- or di-(C_{1-3} alkyl)amino, C_{1-6} alkyl-$S(O)_q$, or halogen;

wherein said cyclic group is optionally attached to a C_{1-4} saturated or unsaturated branched or unbranched carbon chain wherein said carbon chain is in turn covalently attached to Q , said carbon chain is optionally partially or fully halogenated and wherein one or more methylene groups are optionally replaced by O, NH, S(O), $S(O)_2$ or S, wherein said methylene groups are further optionally independently substituted with 1-2 oxo groups and one or more C_{1-4} branched or unbranched alkyl optionally substituted by one or more halogen atoms;

Q is selected from the group consisting of:

a) phenyl, naphthyl, pyridine, pyrimidine, pyridazine, imidazole, benzimidazole, furan, thiophene, pyran, naphthyridine, oxazo[4,5-*b*]pyridine and imidazo[4,5-*b*]pyridine, which are optionally substituted with one to three groups selected from the group consisting of halogen, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy, mono- or di-(C_{1-3} alkyl)amino, C_{1-6} alkyl-$S(O)_m$ and phenylamino wherein the phenyl ring is optionally substituted with one to two groups selected from the group consisting of halogen, C_{1-6} alkyl and C_{1-6} alkoxy;

b) tetrahydropyran, tetrahydrofuran, 1,3-dioxolanone, 1,3-dioxanone, 1,4-dioxane, morpholine, thiomorpholine, thiomorpholine sulfoxide, thiomorpholine sulfone, piperidine, piperidinone, tetrahydropyrimidone, cyclohexanone, cyclohexanol,

pentamethylene sulfide, pentamethylene sulfoxide, pentamethylene sulfone, tetramethylene sulfide, tetramethylene sulfoxide and tetramethylene sulfone which are optionally substituted with one to three groups selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy, mono- or di-(C_{1-3} alkyl)amino-C_{1-3} alkyl, phenylamino-C_{1-3} alkyl and C_{1-3} alkoxy-C_{1-3} alkyl;

c) C_{1-6} alkoxy, secondary or tertiary amine wherein the amino nitrogen is covalently bonded to groups selected from the group consisting of C_{1-3} alkyl and C_{1-5} alkoxyalkyl and phenyl wherein the phenyl ring is optionally substituted with one to two groups selected from the group consisting of halogen, C_{1-6} alkoxy, hydroxy or mono- or di-(C_{1-3} alkyl)amino, C_{1-6} alkyl-$S(O)_r$ and phenyl-$S(O)_t$, wherein the phenyl ring is optionally substituted with one to two groups consisting of halogen, C_{1-6} alkoxy, hydroxy and mono- or di-(C_{1-3} alkyl)amino;

R_1 is selected from the group consisting of:

(a) C_{3-10} branched or unbranched alkyl, which may optionally be partially or fully halogenated, and optionally substituted with one to three phenyl, naphthyl or heterocyclic groups selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl and isothiazolyl; each such phenyl, naphthyl or heterocycle selected from the group hereinabove described, being substituted with 0 to 5 groups selected from the group consisting of halogen, C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated, C_{3-8} cycloalkyl, C_{5-8} cycloalkenyl, hydroxy, cyano, C_{1-3} alkyloxy which is optionally partially or fully halogenated, $NH_2C(O)$ and di(C_{1-3})alkylaminocarbonyl;

(b) C_{3-7} cycloalkyl selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl and bicycloheptanyl, which are optionally partially or fully halogenated and optionally substituted with one to three C_{1-3} alkyl groups, or an analog of such cycloalkyl group wherein one to three ring methylene groups are replaced by groups independently selected from O, S, CHOH, >C=O, >C=S and NH;

(c) C_{3-10} branched alkenyl optionally partially or fully halogenated, and optionally substituted with one to three C_{1-5} branched or unbranched alkyl, phenyl, naphthyl or heterocyclic groups, with each such heterocyclic group being independently selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl and isothiazolyl, and each such phenyl, naphthyl or heterocyclic group being substituted with 0 to 5 groups selected from halogen, C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated, cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl, bicycloheptanyl, hydroxy, cyano, C_{1-3} alkyloxy which is optionally partially or fully halogenated, $NH_2C(O)$ and mono- or di(C_{1-3})alkylaminocarbonyl;

(d) C_{5-7} cycloalkenyl selected from the group consisting of cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, bicyclohexenyl and bicycloheptenyl, wherein such cycloalkenyl group is optionally substituted with one to three C_{1-3} alkyl groups;

(e) cyano; and,

(f) methoxycarbonyl, ethoxycarbonyl and propoxycarbonyl;

R_2 is selected from the group consisting of:

a C_{1-6} branched or unbranched alkyl optionally partially or fully halogenated, acetyl, aroyl, C_{1-4} branched or unbranched alkoxy optionally partially or fully halogenated, halogen, methoxycarbonyl and phenylsulfonyl;

R_3 is selected from the group consisting of:

a) a phenyl, naphthyl or heterocyclic group selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, tetrahydrofuryl, isoxazolyl, isothiazolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, benzoxazolyl, benzisoxazolyl, benzpyrazolyl,

benzothiofuranyl, cinnolinyl, pterindinyl, phthalazinyl, naphthypyridinyl, quinoxalinyl, quinazolinyl, purinyl and indazolyl wherein such phenyl, naphthyl or heterocyclic group is optionally substituted with one to five groups selected from the group consisting of a C_{1-6} branched or unbranched alkyl, phenyl, naphthyl, heterocycle selected from the group hereinabove described, C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated, cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl, bicycloheptanyl, phenyl C_{1-5} alkyl, naphthyl C_{1-5} alkyl, halo, hydroxy, cyano, C_{1-3} alkyloxy which may optionally be partially or fully halogenated, phenyloxy, naphthyloxy, heteraryloxy wherein the heterocyclic moiety is selected from the group hereinabove described, nitro, amino, mono- or di-(C_{1-3})alkylamino, phenylamino, naphthylamino, heterocyclylamino wherein the heterocyclyl moiety is selected from the group hereinabove described, $NH_2C(O)$, a mono- or di-(C_{1-3})alkyl aminocarbonyl, C_{1-5} alkyl-C(O)-C_{1-4} alkyl, amino-C_{1-5} alkyl, mono- or di-(C_{1-3})alkylamino-C_{1-5} alkyl, amino-$S(O)_2$, di-(C_{1-3})alkylamino-$S(O)_2$, R_4-C_{1-5} alkyl, R_5-C_{1-5} alkoxy, R_6-C(O)-C_{1-5} alkyl and R_7-C_{1-5} alkyl-$N(R_8)$-;

b) a fused aryl selected from the group consisting of benzocyclobutanyl, indanyl, indenyl, dihydronaphthyl, tetrahydronaphthyl, benzocycloheptanyl and benzocycloheptenyl, or a fused heterocyclyl selected from cyclopentenopyridine, cyclohexanopyridine, cyclopentanopyrimidine, cyclohexanopyrimidine, cyclopentanopyrazine, cyclohexanopyrazine, cyclopentanopyridazine, cyclohexanopyridazine, cyclopentanoquinoline, cyclohexanoquinoline, cyclopentanoisoquinoline, cyclohexanoisoquinoline, cyclopentanoindole, cyclohexanoindole, cyclopentanobenzimidazole, cyclohexanobenzimidazole, cyclopentanobenzoxazole, cyclohexanobenzoxazole, cyclopentanoimidazole, cyclohexanoimidazole, cyclopentanothiophene and cyclohexanothiophene; wherein the fused aryl or fused heterocyclyl ring is substituted with 0 to 3 groups independently selected from phenyl, naphthyl, heterocyclyl selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl, and isothiazolyl, C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated, halo, cyano, C_{1-3} alkyloxy

which is optionally partially or fully halogenated, phenyloxy, naphthyloxy, heterocyclyloxy wherein the heterocyclyl moiety is selected from the group hereinabove described, nitro, amino, mono- or di-(C_{1-3})alkylamino, phenylamino, naphthylamino, heterocyclylamino wherein the heterocyclyl moiety is selected from the group hereinabove described, $NH_2C(O)$, a mono- or di-(C_{1-3})alkyl aminocarbonyl, C_{1-4} alkyl-OC(O), C_{1-5} alkyl-C(O)-C_{1-4} branched or unbranched alkyl, an amino-C_{1-5} alkyl, mono- or di-(C_{1-3})alkylamino-C_{1-5} alkyl, R_9-C_{1-5} alkyl, R_{10}-C_{1-5} alkoxy, R_{11}–C(O)-C_{1-5} alkyl and R_{12}-C_{1-5} alkyl-N(R_{13})-;

c) cycloalkyl selected from the group consisting of cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl and bicycloheptanyl, wherein the cycloalkyl is optionally partially or fully halogenated and optionally substituted with one to three C_{1-3} alkyl groups;

d) C_{5-7} cycloalkenyl, selected from the group consisting of cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, bicyclohexenyl and bicycloheptenyl, wherein such cycloalkenyl group is optionally substituted with one to three C_{1-3} alkyl groups;

e) acetyl, aroyl, alkoxycarbonylalkyl and phenylsulfonyl; and

f) C_{1-6} branched or unbranched alkyl optionally partially or fully halogenated;

R_1 and R_2 taken together optionally form a fused phenyl or pyridinyl ring;

each R_8 or R_{13} is independently selected from the group consisting of:

hydrogen and C_{1-4} branched or unbranched alkyl optionally partially or fully halogenated;

each R_4, R_5, R_6, R_7, R_9, R_{10}, R_{11} and R_{12} is independently selected from the group consisting of:

morpholine, piperidine, piperazine, imidazole and tetrazole;

m is 0, 1 or 2;

q is 0, 1 or 2;

r is 0, 1 or 2;

t is 0, 1 or 2; and

X is O or S.

The compounds of the invention may be prepared as physiologically and pharmaceutically acceptable salts, as may seem appropriate to one of ordinary skill in the art.

The compounds produced by the novel process of the invention are only those which are contemplated to be 'chemically stable' as will be appreciated by those skilled in the art. For example, a compound which would have a 'dangling valency', or a 'carbanion' are not compounds contemplated to be made by the novel process.

All terms as used herein in this specification, unless otherwise stated, shall be understood in their ordinary meaning as known in the art. For example, "C_{1-4}alkoxy" is a C_{1-4}alkyl with a terminal oxygen, such as methoxy, ethoxy, propoxy, pentoxy and hexoxy. All alkyl, alkenyl and alkynyl groups shall be understood as being branched or unbranched where structurally possible and unless otherwise specified. Other more specific definitions are as follows:

The term "aroyl" as used in the present specification shall be understood to mean "benzoyl" or "naphthoyl".

NMP: 1-methyl-2-pyrrolidinone;

THF: tetrahydrofuran;

DMF: N,N'-dimethylformamide;

DMAC: N-N'-dimethylacetamide;

DMSO: dimethylsulfoxide;

DMAP: 4-dimethylaminopyridine;

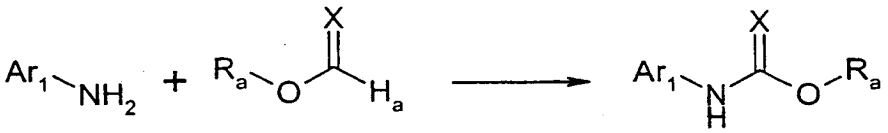
DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene;

PROCESS FOR MAKING COMPOUNDS OF THE FORMULA(I)

The novel process comprises:

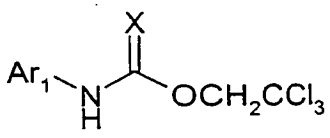
STEP 1:

Reacting in a suitable solvent an amino-heterocycle NH_2-Ar_1 with a haloformate RaOC(X)Ha, wherein Ra represents C_{2-3} halocarbon, preferably 2,2,2-trichloroethyl, and Ha represents halogen, preferably chloro, X is as defined above, in the presence of a suitable base, to produce carbamate of the formula (II):



(II)

Preferable formate RaOC(X)Ha are those, which upon hydrolysis of the formula(II) intermediates, will form a water soluble byproduct which is easily removed by aqueous washing, such byproduct would be, for example, 2,2,2-trichloroethanol. Examples of preferred RaOCOHa are trichloroethyl chloroformate or trichloroethyl chlorothioformate. Accordingly, a preferred compound of the formula(II) is:

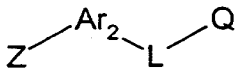


Synthesis of amino-heterocycle NH_2-Ar_1 has been illustrated in US Patent Application No. 09/484,638, incorporated herein by reference. A particularly preferred compound of the formula(II) is where Ar_1 is 1-tolyl-3-*t*-butyl-pyrazole-5-yl.

Reaction conditions such as the selection of a suitable solvent and temperature is within the skill of the ordinary artisan depending on the particular compounds desired. Typically, the reaction of step1 is in a non-aqueous or an aqueous solvent, preferably THF or ethyl acetate, in the presence of a suitable base such as tertiary amine for example triethylamine, diisopropylethylamine, N-methylpyrrolidine, DBU(1,8-diazabicyclo[5.4.0]undec-7-ene), DMAP(4-dimethylaminopyridine), N-methylmorpholine, pyridine, methyl pyridine or inorganic bases such as sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate and potassium bicarbonate. Preferred suitable bases for step 1 are diisopropylethylamine, NaOH or N-methylpyrrolidine. The reaction occurs at a temperature of about 0 – 100°C, preferably 5 – 15 °C, for about 0.5 – 24 hrs, preferably 3-4 hrs.

STEP 2

For certain preferred embodiments, Step 2 proceeds as follows. Reacting a Z-Ar_2-MH, where Z is a nitro or nitroso group, M is O, S, or NH, and Ar_2 is as defined hereinabove, with a Y-J-Q moiety in a suitable solvent to produce the intermediate of formula (III)



(III)

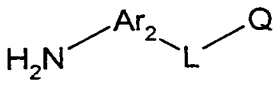
wherein L and Q are as defined hereinabove , Y is a leaving group such as a halogen and M-J constitutes L;

A suitable solvent for the above reaction would be a polar non-protic organic solvent, such as acetonitrile, DMF (N,N'-dimethylformamide), DMAC (N-N'-dimethylacetamide), DMSO (dimethylsulfoxide) and NMP (1-methyl-2-pyrrolidinone), preferably NMP, at a temperature of about 50 – 100 °C, preferably between 75 – 95 °C, for about 0.5-24 hrs, preferably 3-4 hrs.

For other embodiments of L, analogous methods can be found in U.S. Patent Application Nos. 09/484,638 and 09/505,582 incorporated in their entirety by reference.

STEP 3

Reducing compound of formula (III) with catalytic hydrogenation or non-catalytic reduction to produce the intermediate of formula (IV):



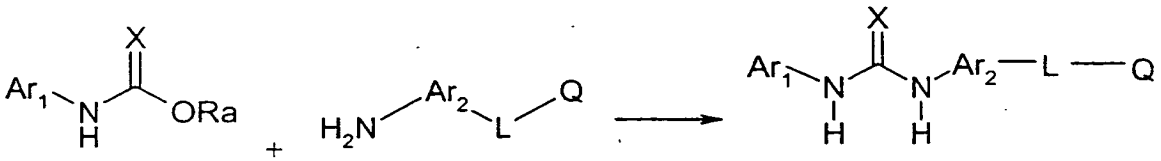
(IV)

Catalytic hydrogenation is preferred, a preferred catalyst is Pd/C. Reaction conditions such as the selection of a suitable solvent and temperature is within the skill of the ordinary artisan. The catalytic hydrogenation with respect to H_2 pressure and time can be varied, a preferable hydrogenation occurs under about 30 psi for about 1 hr - 24 hours.

STEP 4

Reacting the intermediate of formula (II) with the intermediate of formula (IV) with or without base, preferably with a base. A suitable base will be one such as tertiary amine for example triethylamine, diisopropylethylamine, N-methylpyrrolidine, DBU, DMAP, N-methylmorpholine, pyridine, methyl pyridine or an inorganic base such as sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate and potassium bicarbonate. Preferred bases are diisopropylethylamine or N-

methylpyrrolidine. The reaction takes place in the presence of suitable solvent to produce the product of formula (I):



(II) (IV) (I)

Reaction conditions such as the selection of a suitable solvent, base and temperature can be varied according to the specific compound of the formula(I) that is desired. The reaction can be run in a suitable polar, or a suitable non-polar solvent such as methylene chloride or chloroform or in heptane, hexane, cyclohexane, ethyl acetate, benzene, toluene, xylene, tetrahydropfuran, dioxane, ethyl ether, methyl butyl ether or in a biphasic aqueous/organic mixture. Preferably the solvent will be a polar non-protic organic solvent such as NMP(1-methyl-2-pyrrolidinone), acetonitrile, DMF(N,N-dimethylformamide), DMAC(N,N-dimethylacetamide) or DMSO, more preferably DMSO or NMP, which is heated to an appropriate temperature, preferably about 55-60 °C for about 1.5 hours. Particular separation methods depending on the compound desired will be apparent to those of ordinary skill in the art. A preferred method is shown in Example 1 in the present specification.

A preferred subgeneric aspect of the invention comprises a process of producing compounds of the formula(I) wherein Ar_2 is naphthyl, tetrahydronaphthyl, indanyl or indenyl.

A more preferred subgeneric aspect of the invention comprises a process of producing compounds of the formula(I) wherein Ar_2 is naphthyl.

A yet more preferred subgeneric aspect of the invention comprises a process of producing compounds of the formula (I), as described in the immediate previous paragraph, wherein:

Ar_1 is thiophene or pyrazole;

Ar_2 is 1-naphthyl;

L is C_{1-6} saturated or unsaturated branched or unbranched carbon chain wherein one or more methylene groups are optionally independently replaced by O,N or S; and wherein said linking group is optionally substituted with 0-2 oxo groups and one or more C_{1-4} branched or unbranched alkyl optionally substituted by one or more halogen atoms;

or L is cyclopentenyl, cyclohexenyl, cycloheptenyl, each optionally substituted with an oxo group or 1-3 C_{1-4} branched or unbranched alkyl, C_{1-4}alkoxy or C_{1-4}alkylamino; or L is phenyl, pyridine, furan or thiophene each being optionally independently substituted with 1-3 C_{1-4} branched or unbranched alkyl, C_{1-4}alkoxy, hydroxy, cyano, mono- or di-(C_{1-3} alkyl)amino, C_{1-6} alkyl-$S(O)_q$ or halogen;

wherein said cyclic group is optionally attached to a C_{1-4} saturated or unsaturated branched or unbranched carbon chain wherein said carbon chain is in turn covalently attached to Q , said carbon chain is optionally partially or fully halogenated and wherein one or more methylene groups are optionally replaced by O, NH, S(O), $S(O)_2$ or S, wherein said methylene groups are further optionally independently substituted with 1-2 oxo groups and one or more C_{1-4} branched or unbranched alkyl optionally substituted by one or more halogen atoms;

R_1 is C_{3-4}alkyl branched or unbranched, cyclopropyl or cyclohexanyl optionally partially or fully halogenated and optionally substituted with one to three C_{1-3} alkyl groups;

R_3 is selected from the group consisting of C_{1-4}alkyl branched or unbranched optionally partially or fully halogenated, cyclopentanyl optionally partially or fully halogenated and optionally substituted with one to three C_{1-3} alkyl groups,

phenyl, pyridinyl each being optionally substituted with one to five groups selected from the group consisting of a C_{1-6} branched or unbranched alkyl, phenyl, naphthyl, pyridinyl, C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated, cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl, bicycloheptanyl, phenyl C_{1-5} alkyl, naphthyl C_{1-5} alkyl,

halo, hydroxy, cyano, C_{1-3} alkyloxy which may optionally be partially or fully halogenated, phenyloxy, naphthyloxy, pyridinyloxy, nitro, amino, mono- or di-(C_{1-3})alkylamino, phenylamino, naphthylamino, pyridinylamino, $NH_2C(O)$, a mono- or di-(C_{1-3})alkyl aminocarbonyl, C_{1-5} alkyl-C(O)-C_{1-4} alkyl, amino-C_{1-5} alkyl, mono- or di-(C_{1-3})alkylamino-C_{1-5} alkyl, amino-$S(O)_2$, di-(C_{1-3})alkylamino-$S(O)_2$, R_4-C_{1-5}alkyl, R_5-C_{1-5} alkoxy, R_6–C(O)-C_{1-5} alkyl and R_7-C_{1-5} alkyl-$N(R_8)$-; and R_3 is alkoxycarbonylalkyl;

A yet further preferred subgeneric aspect of the invention comprises a process of producing compounds of the formula (I), as described in the immediate previous paragraph, wherein Ar_1 is pyrazole.

A still yet further preferred subgeneric aspect of the invention comprises a process of producing compounds of the formula (I), as described in the immediate previous paragraph, wherein L is C_{1-5} saturated carbon chain wherein one or more methylene groups are optionally independently replaced by O,N or S; and wherein said linking group is optionally substituted with 0-2 oxo groups and one or more C_{1-4} branched or unbranched alkyl optionally substituted by one or more halogen atoms;

More particularly preferred embodiments of the process of the invention is where L is propoxy, ethoxy, methoxy, methyl, propyl, C_{3-5} acetylene or methylamino each being optionally substituted as described herein and Q is morpholine.

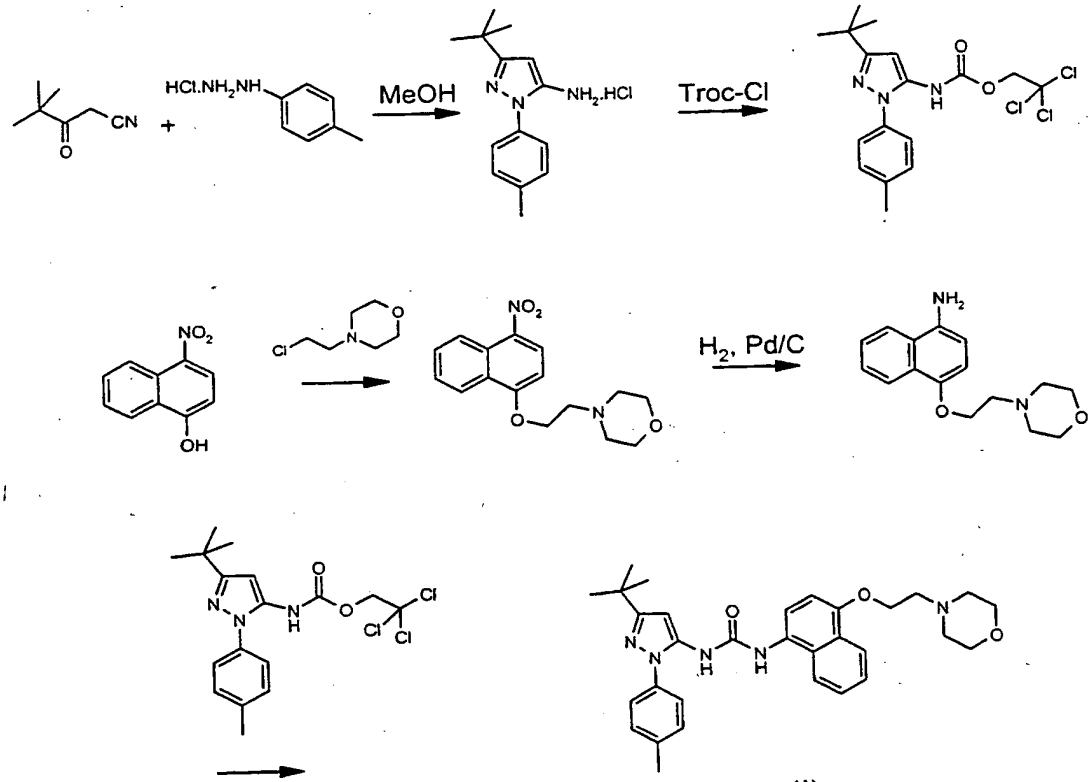
A even more particularly preferred embodiment of L is ethoxy optionally substituted, the base is diisopropylethylamine and the polar non-protic organic solvent is DMSO.

In order that this invention be more fully understood, the following examples are set forth. These examples are for the purpose of illustrating preferred embodiments of this invention, and are not to be construed as limiting the scope of the invention in any way.

SYNTHETIC EXAMPLES

EXAMPLE 1

1-[3-tert-butyl-1-p-tolyl-1H-pyrazol-5-yl]-3-[4-(2-morpholin-4-yl-ethoxy)naphthalen-1-yl]-urea.



5-Amino-3-*t*-butyl-1-*p*-tolylpyrazole hydrochloride: A solution of pivaloylacetonitrile (750 g, 6.0 mol) and *p*-tolylhydrazine hydrochloride (660 g, 4.2 mol) in methanol (2.8 L) was refluxed for 3 h. Heptane was added, and methanol was removed by distillation. The product was crystallized from the solution, collected by filtration and dried in vacuum oven to constant weight. Yield: 1.05 kg, 94%. ^{1}H NMR δ ($CDCl_3$) 7.50 (d, 2H), 7.30 (d, 2H), 5.60 (s, 1H), 2.45 (s, 3H), 1.40 (s, 9H). MS (CI) *m/z* 229 (M^+ + H).

5-(2,2,2-Trichloroethoxycarbonyl)amino-3-*t*-butyl-1-*p*-tolylpyrazole: A mixture of 5-amino-3-*t*-butyl-1-*p*-tolylpyrazole hydrochloride (300 g, 1.13 mol), water (0.9 L), EtOAc (2.1 L) and NaOH (117 g, 2.84 mol) was stirred between 5 –15 ^{0}C for 30 min. To this mixture, 2,2,2-trichloroethyl chloroformate (342 g, 1.58 mol) was added over 1 h between 5 – 15 ^{0}C. The mixture was stirred at room temperature for 2 h, and then the aqueous layer was separated from the EtOAc layer. The EtOAc layer was washed with brine (2 x 0.9 L) and dried over $MgSO_4$ (60 g). The EtOAc layer was collected by filtration. To this solution, heptane was added. A part of the solution was removed by distillation. The product was crystallized from the solution, collected by filtration and dried in vacuum oven to constant weight. Yield: 409 g, 90%. ^{1}H NMR ($CDCl_3$) δ 7.40 (d, 2H), 7.30 (d, 2H), 6.40 (s, 1H), 4.80 (s, 2H), 2.40 (s, 3H), 1.40 (s, 9H). MS (EI) *m/z* 404 (M^+).

4-Nitro-1-(2-morpholinethoxy)naphthalene: A mixture of 4-nitro-1-hydroxynaphthalene (194 g, 1.0 mol), 4-(2-chloroethyl)morpholine hydrochloride (264 g, 1.4 mol), NaOH (58 g, 1.4 mol), K_2CO_3 (339 g, 2.4 mol) and 1-methyl-2-pyrrolidinone (1.0 L) was heated to 90 – 100 ^{0}C and held for 1 – 2 h. The mixture was cooled to 40 ^{0}C and water was slowly added. The mixture was cooled to 5 ^{0}C and held for 4 h. The product was collected by filtration, washed with water, cyclohexane and dried in vacuum to constant weight. Yield: 227 g, 75%. ^{1}H NMR ($CDCl_3$) δ 8.76 (d, 1H), 8.38 (m, 2H), 7.74 (dd, 1H), 7.58 (dd, 1 H), 6.79 (d, 1 H), 4.38 (dd, 2 H), 3.74 (d, 4 H), 2.98 (dd, 2H), 2.65 (d, 4 H). MS (EI) *m/z* 303 (M + 1).

4-Amino-1-(2-morpholinethoxy)naphthalene hydrochloride: A mixture of 4-nitro-1-(2-morpholinethoxy)naphthalene (40 g, 0.13 mol), MeOH (280 mL) and Pd/C (50% water, 1.2 g) was hydrogenated under 30 psi for 24 h. The catalyst was filtered through a layer of diatomaceous earth under nitrogen. To this filtrate 20 mL of HCl (37%) and cyclohexane (200 mL) were added. The solvent was removed under reduced pressure and the product collected by filtration. The product was dried in vacuum to constant weight. Yield: 33 g, 82%. ^{1}H NMR (DMSO) δ 8.38 (d, 1H), 8.00 (d, 1H), 7.72 (dd, 1H),

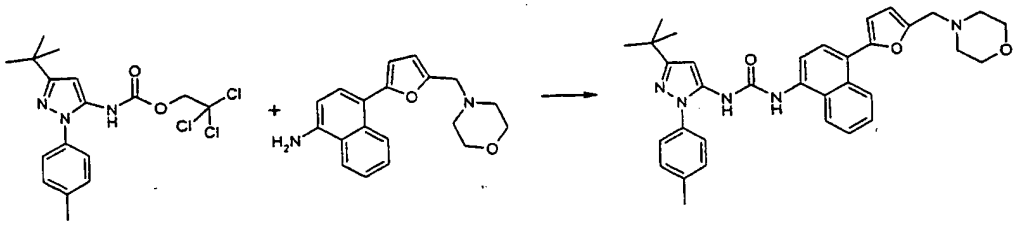
7.64 (m, 2H), 7.05 (d, 1H), 4.62 (s, 2H), 4.00 (b, 4H), 3.88 (s, 2H), 3.40 (b, 4H). MS (EI) *m/z* 273 (M^+).

1-[3-tert-butyl-1-p-tolyl-1H-pyrazol-5-yl]-3-[4-(2-morpholin-4-yl-ethoxy)naphthalen-1-yl]-urea: A solution of 5-(2,2,2-trichloroethoxycarbonyl)amino-3-*t*-butyl-1-*p*-tolylpyrazole (10.6 g, 26 mmol), 4-amino-1-(2-morpholinethoxy)naphthalene (free base from HCl salt above, 7.16 g, 26 mmol), diisopropylethylamine (3.2 g, 25 mmol) and DMSO (75 mL) was heated to 55 – 60 ^{0}C and held for 1.5 h. To this solution, ethyl acetate (100 mL) was added. The organic layer was washed with brine (4x50 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure, and residue was crystallized from acetonitrile (50 mL) at 0 ^{0}C. The product was collected by filtration, recrystallized from isopropanol and dried in vacuum to constant weight, m.p.: 151-152 °C. Yield: 11.4g, 87%. ^{1}H NMR (DMSO) δ 8.75 (s, 1H), 8.51 (s, 1H), 8.21 (d, 1H), 7.85 (d, 1H), 7.65 (d, 1H), 7.55 (m, 2H), 7.49 (dd, 1H), 7.35 (dd, 1H), 6.95 (d, 1H), 6.38 (s, 1H), 4.26 (dd, 2H), 3.60 (dd, 4H), 2.81 (dd, 2H), 2.55 (dd, 4H), 2.38 (s, 3H), 1.29 (s, 9H). MS (CI) *m/z* 528 (M^++1).

The following additional non-limiting examples can be made using the novel process of the invention:

EXAMPLE 2

1-[3-tert-butyl-1-p-tolyl-1H-pyrazol-5-yl]-3-{4-[5-(morpholin-4-ylmethyl)fur-2-yl]naphthalen-1-yl} urea:

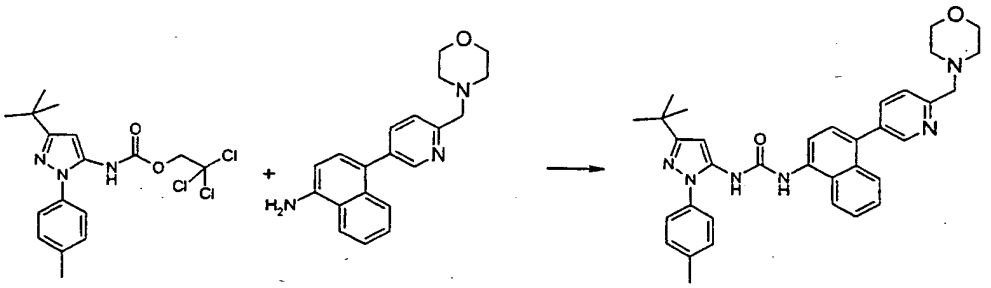


A solution of 5-(2,2,2-trichloroethoxycarbonyl)amino-3-*t*-butyl-1-*p*-tolylpyrazole (26 mmol), 1-amino-4-[5-(morpholin-4-ylmethyl)fur-2-yl]naphthalene (26 mmol),

diisopropylethylamine (25 mmol) and DMSO (75 mL) is heated to 55 – 90^{0}C and held for 2-8 h. To this solution, ethyl acetate (100 mL) is added. The organic layer is washed with brine (4x50 mL), and dried over $MgSO_4$. The solvent is removed under reduced pressure, and residue is crystallized from a suitable solvent such as acetonitrile (50 mL) at 0 ^{0}C. The product is collected by filtration and recrystallized from a suitable solvent such as isopropanol and dried in vacuum to constant weight.

EXAMPLE 3

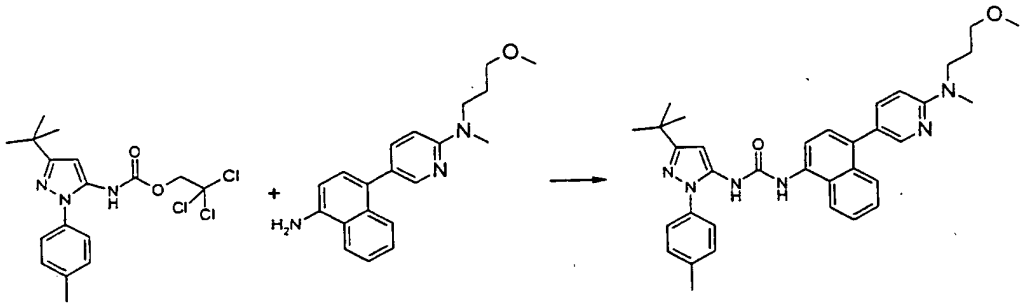
1-[3-tert-butyl-1-p-tolyl-1H-pyrazol-5-yl]-3-{4-[6-(morpholin-4-ylmethyl)pyridin-3-yl]naphthalen-1-yl} urea:



A solution of 5-(2,2,2-trichloroethoxycarbonyl)amino-3-*t*-butyl-1-*p*-tolylpyrazole (26 mmol), 1-amino-4-[6-(morpholin-4-ylmethyl)pyridin-3-yl]naphthalene (26 mmol), diisopropylethylamine (25 mmol) and DMSO (75 mL) is heated to 55 – 90^{0}C and held for 2-8 h. To this solution, ethyl acetate (100 mL) is added. The organic layer is washed with brine (4x50 mL), and dried over $MgSO_4$. The solvent is removed under reduced pressure, and residue is crystallized from a suitable solvent such as acetonitrile (50 mL) at 0 ^{0}C. The product is collected by filtration and recrystallized from a suitable solvent such as isopropanol and dried in vacuum to constant weight.

EXAMPLE 4

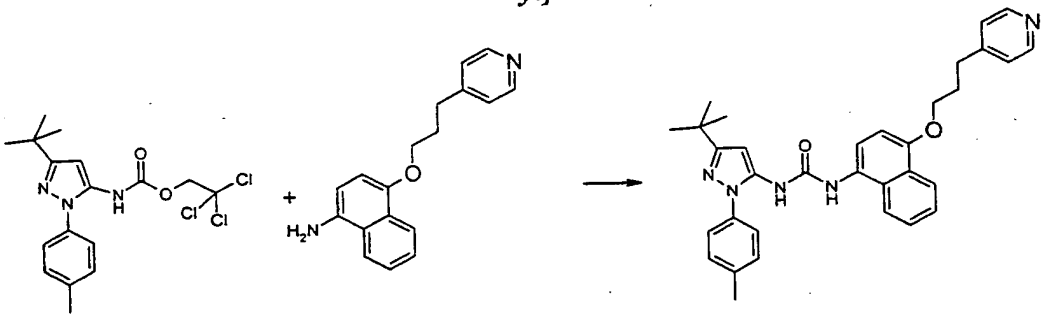
1-[3-tert-butyl-1-p-tolyl-1H-pyrazol-5-yl]-3-(4-{6-[(3-methoxypropyl)methylamino]pyridin-3-yl}naphthalen-1-yl)urea



A solution of 5-(2,2,2-trichloroethoxycarbonyl)amino-3-*t*-butyl-1-*p*-tolylpyrazole (26 mmol), 1-amino-4-{6-[(3-methoxypropyl)methylamino]pyridin-3-yl}naphthalene (26 mmol), diisopropylethylamine (25 mmol) and DMSO (75 mL) is heated to 55 – 90^{0}C and held for 2-8 h. To this solution, ethyl acetate (100 mL) is added. The organic layer is washed with brine (4x50 mL), and dried over $MgSO_4$. The solvent is removed under reduced pressure, and residue is crystallized from a suitable solvent such as acetonitrile (50 mL) at 0 ^{0}C. The product is collected by filtration and recrystallized from a suitable solvent such as isopropanol and dried in vacuum to constant weight.

EXAMPLE 5

1-[3-tert-butyl-1-p-tolyl-1H-pyrazol-5-yl]-3-[4-(3-pyridin-4-yl-propoxy)naphthalen-1-yl]-urea

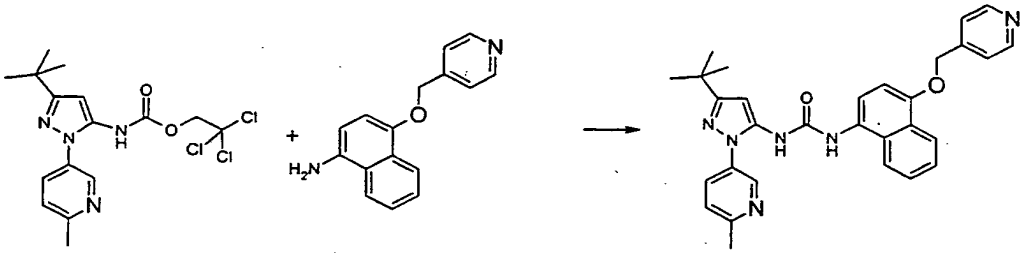


A solution of 5-(2,2,2-trichloroethoxycarbonyl)amino-3-*t*-butyl-1-*p*-tolylpyrazole (26 mmol), 1-amino-4-(3-pyridin-4-ylpropoxy)naphthalene (26 mmol), diisopropylethylamine (25 mmol) and DMSO (75 mL) is heated to 55 – 90^{0}C and held for 2-8 h. To this solution, ethyl acetate (100 mL) is added. The organic layer is washed with brine (4x50 mL), and dried over $MgSO_4$. The solvent is removed under reduced pressure, and residue is crystallized from a suitable solvent such as acetonitrile (50 mL)

at 0 ^{0}C. The product is collected by filtration and recrystallized from a suitable solvent such as isopropanol and dried in vacuum to constant weight.

EXAMPLE 6

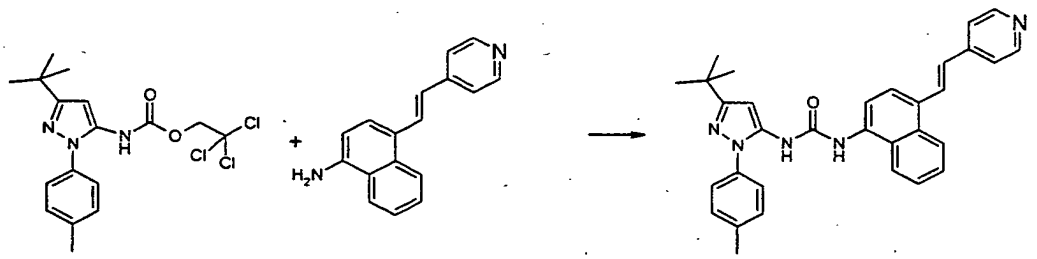
1-[3-tert-butyl-1-(2-methylpyridin-5-yl)-1H-pyrazol-5-yl]-3-[4-(pyridin-4-yl-methoxy)naphthalen-1-yl]-urea



A solution of 5-(2,2,2-trichloroethoxycarbonyl)amino-3-*t*-butyl-1-(2-methylpyridin-5-yl)pyrazole (26 mmol), 1-amino-4-(pyridin-4-ylmethoxy)naphthalene (26 mmol), diisopropylethylamine (25 mmol) and DMSO (75 mL) is heated to 55 – 90^{0}C and held for 2-8 h. To this solution, ethyl acetate (100 mL) is added. The organic layer is washed with brine (4x50 mL), and dried over $MgSO_4$. The solvent is removed under reduced pressure, and residue is crystallized from a suitable solvent such as acetonitrile (50 mL) at 0 ^{0}C. The product is collected by filtration and recrystallized from a suitable solvent such as isopropanol and dried in vacuum to constant weight.

EXAMPLE 7

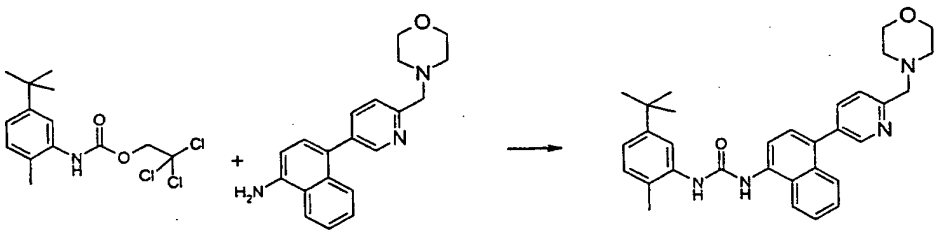
1-[3-tert-butyl-1-p-tolyl-1H-pyrazol-5-yl]-3-[4-(2-pyridin-4-yl-ethenyl)naphthalen-1-yl]-urea



A solution of 5-(2,2,2-trichloroethoxycarbonyl)amino-3-*t*-butyl-1-*p*-tolylpyrazole (26 mmol), 1-amino-4-(2-pyridin-4-yl-ethenyl)naphthalene (26 mmol), diisopropylethylamine (3.2 g, 25 mmol) and DMSO (75 mL) is heated to 55 – 90^{0}C and held for 2-8 h. To this solution, ethyl acetate (100 mL) is added. The organic layer is washed with brine (4x50 mL), and dried over $MgSO_4$. The solvent is removed under reduced pressure, and residue is crystallized from a suitable solvent such as acetonitrile (50 mL) at 0 ^{0}C. The product is collected by filtration and recrystallized from a suitable solvent such as isopropanol and dried in vacuum to constant weight.

EXAMPLE 8

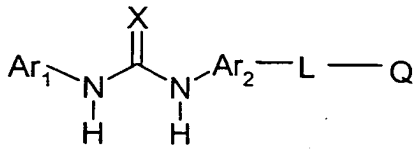
1-(5-tert-Butyl-2-methyphenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]urea:



A solution of 5-*t*-butyl-2-methyl-1-(2,2,2-trichloroethoxycarbonyl)aminobenzene (26 mmol), 1-amino-4-[6-(morpholin-4-ylmethyl)pyridin-3-yl]naphthalene (26 mmol), diisopropylethylamine (3.2 g, 25 mmol) and DMSO (75 mL) is heated to 55 – 60 ^{0}C and held for 1.5 h. To this solution, ethyl acetate (100 mL) is added. The organic layer is washed with brine (4x50 mL), and dried over $MgSO_4$. The solvent is removed under reduced pressure, and residue is crystallized from a suitable solvent such as acetonitrile (50 mL) at 0 ^{0}C. The product is collected by filtration and recrystallized from a suitable solvent such as isopropanol and dried in vacuum to constant weight.

What is Claimed is:

1. A process for producing a compound of the formula (I):



(I)

wherein:

Ar_1 is a heterocyclic group selected from the group consisting of phenyl, pyridine, pyridone, pyrrole, pyrrolidine, pyrazole, imidazole, oxazole, thiazole, furan and thiophene;

wherein Ar_1 is optionally substituted by one or more R_1, R_2 or R_3;

Ar_2 is:

phenyl, naphthyl, quinoline, isoquinoline, tetrahydronaphthyl, tetrahydroquinoline, tetrahydroisoquinoline, benzimidazole, benzofuran, indanyl, indenyl or indole each being optionally substituted with one to three R_2 groups;

L, a linking group, is:

C_{1-10} saturated or unsaturated branched or unbranched carbon chain;

wherein one or more methylene groups are optionally independently replaced by O,N or S; and

wherein said linking group is optionally substituted with 0-2 oxo groups and one or more C_{1-4} branched or unbranched alkyl optionally substituted by one or more halogen atoms;

or L is a cyclic group which is:

a) a C_{5-8} cycloalkyl or cycloalkenyl optionally substituted with 1-2 oxo groups, 1-3 C_{1-4} branched or unbranched alkyl, C_{1-4} alkoxy or C_{1-4} alkylamino chains;

b) phenyl, furan, thiophene, pyrrole, imidazolyl, pyridine, pyrimidine, pyridinone, dihydropyridinone, maleimide, dihydromaleimide, piperdine, piperazine or pyrazine each

being optionally independently substituted with 1-3 C_{1-4} branched or unbranched alkyl, C_{1-4}alkoxy, hydroxy, cyano, mono- or di-(C_{1-3} alkyl)amino, C_{1-6} alkyl-$S(O)_q$, or halogen;

wherein said cyclic group is optionally attached to a C_{1-4} saturated or unsaturated branched or unbranched carbon chain wherein said carbon chain is in turn covalently attached to Q , said carbon chain is optionally partially or fully halogenated and wherein one or more methylene groups are optionally replaced by O, NH, S(O), $S(O)_2$ or S, wherein said methylene groups are further optionally independently substituted with 1-2 oxo groups and one or more C_{1-4} branched or unbranched alkyl optionally substituted by one or more halogen atoms;

Q is selected from the group consisting of:

a) phenyl, naphthyl, pyridine, pyrimidine, pyridazine, imidazole, benzimidazole, furan, thiophene, pyran, naphthyridine, oxazo[4,5-*b*]pyridine and imidazo[4,5-*b*]pyridine, which are optionally substituted with one to three groups selected from the group consisting of halogen, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy, mono- or di-(C_{1-3} alkyl)amino, C_{1-6} alkyl-$S(O)_m$ and phenylamino wherein the phenyl ring is optionally substituted with one to two groups selected from the group consisting of halogen, C_{1-6} alkyl and C_{1-6} alkoxy;

b) tetrahydropyran, tetrahydrofuran, 1,3-dioxolanone, 1,3-dioxanone, 1,4-dioxane, morpholine, thiomorpholine, thiomorpholine sulfoxide, thiomorpholine sulfone, piperidine, piperidinone, tetrahydropyrimidone, cyclohexanone, cyclohexanol, pentamethylene sulfide, pentamethylene sulfoxide, pentamethylene sulfone, tetramethylene sulfide, tetramethylene sulfoxide and tetramethylene sulfone which are optionally substituted with one to three groups selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy, mono- or di-(C_{1-3} alkyl)amino-C_{1-3} alkyl, phenylamino-C_{1-3} alkyl and C_{1-3} alkoxy-C_{1-3} alkyl;

c) C_{1-6} alkoxy, secondary or tertiary amine wherein the amino nitrogen is covalently bonded to groups selected from the group consisting of C_{1-3} alkyl and C_{1-5} alkoxyalkyl and phenyl wherein the phenyl ring is optionally substituted with one to two groups selected from the group consisting of halogen, C_{1-6} alkoxy, hydroxy or mono- or di-

(C_{1-3} alkyl)amino, C_{1-6} alkyl-$S(O)_r$ and phenyl-$S(O)_t$, wherein the phenyl ring is optionally substituted with one to two groups consisting of halogen, C_{1-6} alkoxy, hydroxy and mono- or di-(C_{1-3} alkyl)amino;

R_1 is selected from the group consisting of:

a) C_{3-10} branched or unbranched alkyl, which may optionally be partially or fully halogenated, and optionally substituted with one to three phenyl, naphthyl or heterocyclic groups selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl and isothiazolyl; each such phenyl, naphthyl or heterocycle selected from the group hereinabove described, being substituted with 0 to 5 groups selected from the group consisting of halogen, C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated, C_{3-8} cycloalkyl, C_{5-8} cycloalkenyl, hydroxy, cyano, C_{1-3} alkyloxy which is optionally partially or fully halogenated, $NH_2C(O)$ and di(C_{1-3})alkylaminocarbonyl;

b) C_{3-7} cycloalkyl selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl and bicycloheptanyl, which are optionally partially or fully halogenated and optionally substituted with one to three C_{1-3} alkyl groups, or an analog of such cycloalkyl group wherein one to three ring methylene groups are replaced by groups independently selected from O, S, CHOH, >C=O, >C=S and NH;

c) C_{3-10} branched alkenyl which may optionally be partially or fully halogenated, and which optionally be substituted with one to three C_{1-5} branched or unbranched alkyl, phenyl, naphthyl or heterocyclic groups, with each such heterocyclic group being independently selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl and isothiazolyl, and each such phenyl, naphthyl or heterocyclic group being substituted with 0 to 5 groups selected from halogen, C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated, cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl, bicycloheptanyl,

hydroxy, cyano, C_{1-3} alkyloxy which is optionally partially or fully halogenated, $NH_2C(O)$ and mono- or di(C_{1-3})alkylaminocarbonyl;

d) C_{5-7} cycloalkenyl selected from the group consisting of cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, bicyclohexenyl and bicycloheptenyl, wherein such cycloalkenyl group is optionally be substituted with one to three C_{1-3} alkyl groups;

e) cyano; and,

f) methoxycarbonyl, ethoxycarbonyl and propoxycarbonyl;

R_2 is selected from the group consisting of:

a C_{1-6} branched or unbranched alkyl optionally partially or fully halogenated, acetyl, aroyl, C_{1-3} branched or unbranched alkoxy optionally partially or fully halogenated, halogen, methoxycarbonyl and phenylsulfonyl;

R_3 is selected from the group consisting of:

a) a phenyl, naphthyl or heterocyclic group selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, tetrahydrofuryl, isoxazolyl, isothiazolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, benzoxazolyl, benzisoxazolyl, benzpyrazolyl, benzothiofuranyl, cinnolinyl, pterindinyl, phthalazinyl, naphthypyridinyl, quinoxalinyl, quinazolinyl, purinyl and indazolyl wherein such phenyl, naphthyl or heterocyclic group is optionally substituted with one to five groups selected from the group consisting of a C_{1-6} branched or unbranched alkyl, phenyl, naphthyl, heterocycle selected from the group hereinabove described, C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated, cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl, bicycloheptanyl, phenyl C_{1-5} alkyl, naphthyl C_{1-5} alkyl, halo, hydroxy, cyano, C_{1-3} alkyloxy which may optionally be partially or fully halogenated,

phenyloxy, naphthyloxy, heteraryloxy wherein the heterocyclic moiety is selected from the group hereinabove described, nitro, amino, mono- or di-(C_{1-3})alkylamino, phenylamino, naphthylamino, heterocyclylamino wherein the heterocyclyl moiety is selected from the group hereinabove described, $NH_2C(O)$, a mono- or di-(C_{1-3})alkyl aminocarbonyl, C_{1-5} alkyl-C(O)-C_{1-4} alkyl, amino-C_{1-5} alkyl, mono- or di-(C_{1-3})alkylamino-C_{1-5} alkyl, amino-$S(O)_2$, di-(C_{1-3})alkylamino-$S(O)_2$, R_4-C_{1-5}alkyl, R_5-C_{1-5} alkoxy, R_6–C(O)-C_{1-5} alkyl and R_7-C_{1-5} alkyl-N(R_8)-;

b) a fused aryl selected from the group consisting of benzocyclobutanyl, indanyl, indenyl, dihydronaphthyl, tetrahydronaphthyl, benzocycloheptanyl and benzocycloheptenyl, or a fused heterocyclyl selected from cyclopentenopyridine, cyclohexanopyridine, cyclopentanopyrimidine, cyclohexanopyrimidine, cyclopentanopyrazine, cyclohexanopyrazine, cyclopentanopyridazine, cyclohexanopyridazine, cyclopentanoquinoline, cyclohexanoquinoline, cyclopentanoisoquinoline, cyclohexanoisoquinoline, cyclopentanoindole, cyclohexanoindole, cyclopentanobenzimidazole, cyclohexanobenzimidazole, cyclopentanobenzoxazole, cyclohexanobenzoxazole, cyclopentanoimidazole, cyclohexanoimidazole, cyclopentanothiophene and cyclohexanothiophene; wherein the fused aryl or fused heterocyclyl ring is substituted with 0 to 3 groups independently selected from phenyl, naphthyl, heterocyclyl selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl, and isothiazolyl, C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated, halo, cyano, C_{1-3} alkyloxy which is optionally partially or fully halogenated, phenyloxy, naphthyloxy, heterocyclyloxy wherein the heterocyclyl moiety is selected from the group hereinabove described, nitro, amino, mono- or di-(C_{1-3})alkylamino, phenylamino, naphthylamino, heterocyclylamino wherein the heterocyclyl moiety is selected from the group hereinabove described, $NH_2C(O)$, a mono- or di-(C_{1-3})alkyl aminocarbonyl, C_{1-4} alkyl-OC(O), C_{1-5} alkyl-C(O)-C_{1-4} branched or unbranched alkyl, an amino-C_{1-5} alkyl, mono- or di-(C_{1-3})alkylamino-C_{1-5} alkyl, R_9-C_{1-5} alkyl, R_{10}-C_{1-5} alkoxy, R_{11}–C(O)-C_{1-5} alkyl and R_{12}-C_{1-5} alkyl-N(R_{13})-;

c) cycloalkyl selected from the group consisting of cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl and bicycloheptanyl, wherein the cycloalkyl is optionally partially or fully halogenated and optionally substituted with one to three C_{1-3} alkyl groups;

d) C_{5-7} cycloalkenyl, selected from the group consisting of cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, bicyclohexenyl and bicycloheptenyl, wherein such cycloalkenyl group is optionally substituted with one to three C_{1-3} alkyl groups;

e) acetyl, aroyl, alkoxycarbonylalkyl and phenylsulfonyl; and

f) C_{1-6} branched or unbranched alkyl optionally partially or fully halogenated;

R_1 and R_2 taken together optionally form a fused phenyl or pyridinyl ring;

each R_8 and R_{13} is independently selected from the group consisting of:

hydrogen and C_{1-4} branched or unbranched alkyl optionally partially or fully halogenated;

each R_4, R_5, R_6, R_7, R_9, R_{10}, R_{11} and R_{12} is independently selected from the group consisting of:
morpholine, piperidine, piperazine, imidazole and tetrazole;

m is 0, 1 or 2;

r is 0, 1 or 2;

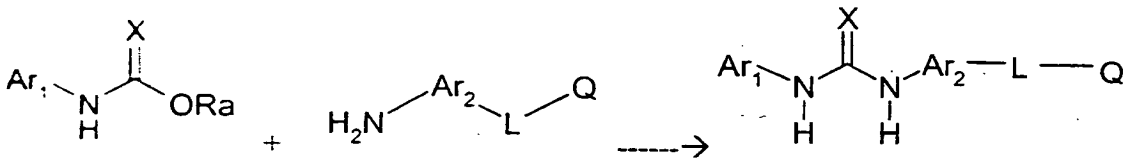
q is 0, 1 or 2;

t is 0, 1 or 2; and

X is O or S;

said process comprising:

reacting of intermediate of formula (II) with intermediate of formula (IV) in the presence of a suitable base said reaction taking place in a suitable solvent at a suitable temperature for a reaction time of about 1.5 hours:



(II) (IV) (I)

wherein Ra is a C_{2-3} halocarbon, Ar_1, Ar_2, X, L and Q are as defined hereinabove; to produce a compound of formula (I).

2. The process according to claim 1 wherein

Ra is 2,2,2-trichloroethyl;

the organic solvent is a polar non-protic solvent selected from the group consisting of NMP, acetonitrile, DMF, DMAC and DMSO;

the base is selected from the group consisting of triethylamine, diisopropylethylamine, N-methylpyrrolidine, DBU, DMAP, N-methylmorpholine, pyridine, methyl pyridine and an inorganic base;

the temperature is about 55-60^{0}C;

Ar_2 is selected from the group consisting of naphthyl, tetrahydronaphthyl, indanyl and indenyl, and

X is O.

3. The process according to claim 2 wherein

Ar_2 is naphthyl;

the polar non-protic organic solvent is selected from the group consisting of NMP and DMSO; and

the base is selected from the group consisting of diisopropylethylamine and N-methylpyrrolidine.

4. The process according to claim 3 wherein

Ar_1 is thiophene or pyrazole;

Ar_2 is 1-naphthyl;

L is C_{1-6} saturated or unsaturated branched or unbranched carbon chain wherein one or more methylene groups are optionally independently replaced by O,N or S; and wherein said linking group is optionally substituted with 0-2 oxo groups and one or more C_{1-4} branched or unbranched alkyl optionally substituted by one or more halogen atoms;

or L is cyclopentenyl, cyclohexenyl or cycloheptenyl each optionally substituted with an oxo group or 1-3 C_{1-4} branched or unbranched alkyl, C_{1-4}alkoxy or C_{1-4}alkylamino; or L is phenyl, pyridine, furan or thiophene each being optionally independently substituted with 1-3 C_{1-4} branched or unbranched alkyl, C_{1-4}alkoxy, hydroxy, cyano, mono- or di-(C_{1-3} alkyl)amino, C_{1-6} alkyl-$S(O)_q$ or halogen;

wherein said cyclic group is optionally attached to a C_{1-4} saturated or unsaturated branched or unbranched carbon chain wherein said carbon chain is in turn covalently attached to Q , said carbon chain is optionally partially or fully halogenated and wherein one or more methylene groups are optionally replaced by O, NH, S(O), $S(O)_2$ or S, wherein said methylene groups are further optionally independently substituted with 1-2 oxo groups and one or more C_{1-4} branched or unbranched alkyl optionally substituted by one or more halogen atoms;

R_1 is C_{3-4}alkyl branched or unbranched, cyclopropyl or cyclohexanyl optionally partially or fully halogenated and optionally substituted with one to three C_{1-3} alkyl groups;

R_3 is selected from the group consisting of C_{1-4}alkyl branched or unbranched optionally partially or fully halogenated;

cyclopentanyl optionally partially or fully halogenated and optionally substituted with one to three C_{1-3} alkyl groups;

phenyl, pyridinyl each being optionally substituted with one to five groups selected from the group consisting of a C_{1-6} branched or unbranched alkyl, phenyl, naphthyl, pyridinyl, C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated, cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl, bicycloheptanyl, phenyl C_{1-5} alkyl, naphthyl C_{1-5} alkyl, halo, hydroxy, cyano, C_{1-3} alkyloxy which may optionally be partially or fully halogenated, phenyloxy, naphthyloxy, pyridinyloxy, nitro, amino, mono- or di-(C_{1-3})alkylamino, phenylamino, naphthylamino, pyridinylamino, $NH_2C(O)$, a mono- or di-(C_{1-3})alkyl aminocarbonyl, C_{1-5} alkyl-C(O)-C_{1-4} alkyl, amino-C_{1-5} alkyl, mono- or di-(C_{1-3})alkylamino-C_{1-5} alkyl, amino-$S(O)_2$, di-(C_{1-3})alkylamino-$S(O)_2$, R_4-C_{1-5}alkyl, R_5-C_{1-5} alkoxy, R_6–C(O)-C_{1-5} alkyl and R_7-C_{1-5} alkyl-$N(R_8)$-;

and R_3 is alkoxycarbonylalkyl;

5. The process according to claim 4 wherein Ar_1 is pyrazole.

6. The process according to claim 5 wherein L is C_{1-5} saturated carbon chain wherein one or more methylene groups are optionally independently replaced by O,N or S; and wherein said linking group is optionally substituted with 0-2 oxo groups and one or more C_{1-4} branched or unbranched alkyl optionally substituted by one or more halogen atoms.

7. The process according to claim 5 wherein

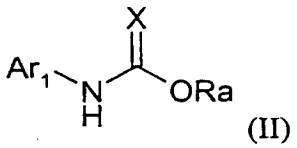
L is propoxy, ethoxy, methoxy, methyl, propyl, C_{3-5} acetylene or methylamino each optionally substituted with 0-2 oxo groups and one or more C_{1-4} branched or unbranched alkyl optionally substituted by one or more halogen atoms; and

Q is morpholine.

7. The process according to claim 6 wherein L is propoxy, ethoxy or methoxy.

8. The process according to claim 7 wherein L is ethoxy, the base is diisopropylethylamine and the polar non-protic organic solvent is DMSO.

9. A process of producing an intermediate compound of the formula(II)



(II)

comprising:

reacting an aminoheterocycle NH_2- Ar_1 with with a formate RaOC(X)Ha, in a suitable solvent in the presence of a suitable base at about 0 to 100^{0}C for about 0.5 to 24 hours, wherein

Ra represents C_{2-3} halocarbon, and Ha represents halogen, X and Ar_1 are as defined in claim 1, to produce carbamate of the formula (II).

10. The process according to claim 9 wherein

Ra is 2,2,2-trichloroethyl,

Ha is chloro,

X is O,

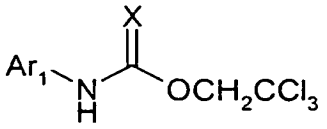
the solvent is THF or ethyl acetate,

the base is selected from the group consisting diisopropylethylamine, N-methylpyrrolidine and NaOH;

the temperature is about 5 to 15^{0}C; and

the time is about 3 hours.

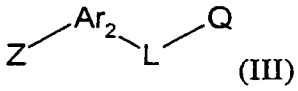
11. A carbamate compound of formula:



wherein Ar_1 is thiophene or pyrazole and X is O.

12. The carbamate compound according to claim 11 wherein Ar_1 is 1-tolyl-3-*t*-butyl-pyrazole-5-yl.

13. A process for producing an intermediate compound of the formula (III)



(III)

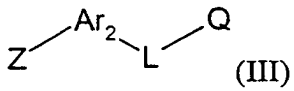
comprising:

reacting a Z-Ar_2-MH compound with a Y-J-Q moiety in a polar non-protic organic solvent at a temperature of about 50-100^{0}C to produce the intermediate with formula (III);

wherein Z is a nitro or nitroso group, M is O, S, or NH, Y is a leaving group, M-J constitutes L; and wherein Ar_2, L and Q are as defined in claim 1.

14. The process according to claim 13 wherein the solvent is selected from the group consisting of acetonitrile, DMF, DMAC, DMSO and NMP and the temperature is about 75-95^{0}C.

15. An intermediate compound of the formula(III):



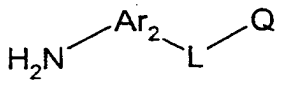
(III)

wherein Z is nitro or nitroso and wherein

Ar_2 is 1-naphthyl,

L is propoxy, ethoxy, methoxy, methyl, propyl, C_{3-5} acetylene or methylamino, and Q is morpholine.

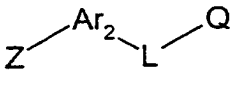
16. A process of producing an intermediate compound of formula (IV):



(IV)

comprising:

reducing compound of formula (III) by catalytic hydrogenation with a Pd/C catalyst under about 30 psi for about 1-24 h:



(III),

wherein Z,Ar_2,L and Q are as defined above in claim 13, to produce the intermediate of formula (IV).

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(30) Priority Data:
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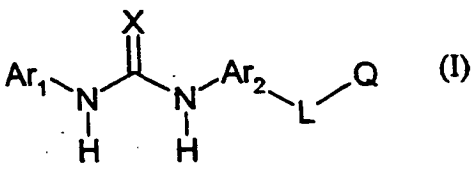
WO 01/04115 A3

(54) Title: NOVEL PROCESS FOR SYNTHESIS OF HETEROARYL-SUBSTITUTED UREA COMPOUNDS



(I)

(57) Abstract: Disclosed are novel processes and novel intermediate compounds for preparing aryl- and heteroaryl-substituted urea compounds of formula (I) wherein Ar_1, Ar_2, L, Q and X are described herein. The product compounds are useful in pharmaceutic compositions for treating diseases or pathological conditions involving inflammation such as chronic inflammatory diseases.

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/US 00/17655

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D231/40 C07D295/08 C07D413/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHONG ET AL.: "Multilevel Selectivity in the mild and high-yielding Chlorosilane-induced Cleavage of Carbamates to Isocyanates" J. ORG. CHEM., vol. 63, 1998, pages 8515-21, XP002155506 Scheme 1 General procedure for the preparation of carbamates 1a-j and 2a-j page 8518, left-hand column Table 1, entry 1g ---	9,10
X	US 4 447 624 A (KRUTAK JAMES J ET AL) 8 May 1984 (1984-05-08) examples 7,8,20,26,27,29,31-36 ---	11
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 December 2000	10. 04 2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Diederen, J

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 291 808 A (ELSLAGER ET AL.) 13 December 1966 (1966-12-13) example 3 ---	16
A	WO 00 43384 A (BOEHRINGER INGELHEIM PHARMA) 27 July 2000 (2000-07-27) Compound LXXII page 55 -----	1

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INTERNATIONAL SEARCH REPORT

ɔrnational application No.
PCT/US 00/17655

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-12

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-12

   A process for producing a compound of the formula I, a process for producing an intermediate carbamate compound of the formula II and the carbamate compound of the formula as presented in claim 11

2. Claims: 13-15

   A process for producing an intermediate compound of the formula III and the intermediate compound III.

3. Claim : 16

   A process of producing an intermediate compound of formula IV.

INTERNATIONAL SEARCH REPORT

Inte tional Application No
PCT/US 00/17655

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4447624 A	08-05-1984	EP 0046694 A JP 57072979 A	03-03-1982 07-05-1982
US 3291808 A	13-12-1966	NONE	
WO 0043384 A	27-07-2000	AU 1752200 A	07-08-2000

Form PCT/ISA/210 (patent family annex) (July 1992)